THE INFLUENCE OF THROMBOSIS IN THE INTRAHEPATIC PORTAL VEIN UPON THE OCCURRENCE OF THE HEPATIC NECROSIS DUE TO THE INTERRUPTION OF THE HEPATIC ARTERY BLOOD FLOW

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Received for publication Sept. 2, 1960

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CHAPTER I INTRODUCTION

Members of our clinic have pointed out (1) that after the ligation of the hepatic arterics, the portal circulation and hypoxic liver necrosis caused by the portal circulation impediment exercises the greatest and the most important influence upon the prognosis of the operated animal, and (2) that administration of penicillin, abbreviated to Pc, and other antibiotics remarkably reduces the mortality rate. Clinical application of this method of the ligation, however, requires further serious considerations of various kinds as cases differ. Particularly, it should always be taken into consideration whether before the ligation there already exist any factors that develop post-operative disturbances of the portal blood flow.

The present experiments have been undertaken in order to observe how the interruption of the hep. aa. is influenced by portal vein thrombosis, which is the most typical cases of portal circulation impediment, especially by infectious thrombosis which is of clinical importance.

CHAPTER II PRELIMINARY EXPERIMENT

— Portal Circulation Impediment without Infection —

I Method

The following various methods were employed. In adult dogs, after an artificial

non-infectious obstruction of the intrahepatic portal vein was produced, the hepatic arterial supply was interrupted, and their prognosis were pursued. In this experiment, non-infectious obstruction was produced in order to exclude all the complicated influences which might be caused by bacterial infection, and to observe only hemodynamic changes caused by the artificially produced obstruction of the portal circulation.

In both the preliminary and the main experiments, healthy adult mongrel dogs, weighing 5.2 to 15.2 kg, were used. In all the dogs 0.5 cc per kg of Nembutal was used for anesthesia.

1. Method of Producing Portal Circulation Impediment

The following methods were employed in producing circulation impediment in the proximal, middle and peripheral parts of the intrahepatic portal vein.

1) Ligation of a portal branch

One portal branch was ligated near where it arises from the portal trunk, instead of producing a thrombus there. Thus, hemodynamically, the same condition as thrombosis was obtained.

2) Injection of Foreign Bodies into the Portal Vein

a) Millet Seeds: Physiologic saline solution containing millet seeds without chaffs (about 2 mm in diameter) was injected into the portal vein by way of the mesentric vein so that they may stay as emboli in the middle portions of the intrahepatic portal vein (GLISSON's capsules).

b) Lycopodia: Physiologic saline solution saturated with lycopodia was injected through the mesentric vein to produce emboli in the peripheral parts of the intrahepatic portal vein (chiefly in lobules).

2. Method of Ligation of the Hep. Aa.

The method of the ligation of the 3 hep. aa., as has hitherto been employed in our clinic, was also employed in the present experiment. The common hep. a., the gastroduodenal a., and the right gastric a. were doubly ligated and severed to interrupt almost whole arterial supply to the liver. After the ligation 100,000 units of Pc was injected in the peritoneal cavity.

II Results

1. Dogs with Ligation of a Portal Branch (Table 1) (Fig. 1)

In No. 56 dog only one of the portal branches coursing leftward was ligated, the hepatic aa. being left intact. The dog survived very well. After a month the liver was taken out with such scarred atrophy in the anterior half of the left superior lobe that it looked almost disappearing. Histological examinations revealed scattered congestion or hemorrhagic necrosis and organized granular tissue growing

Table 1 Dogs with ligation of a portal branch

Dog No.	Weight	Sex	Method of Ligation	Days passed until death	Result
30	9.0 kg	♀	Ligation of left portal branch and 3 hep. aa.	15 days	Sacrifice
35	15.2	♂	Ligation of right portal branch and 3 hep. aa.	2	Death
56	9.5	♂	Ligation of left portal branch	32	Sacrifice

around GLISSON's capsules to repair the damage.

In No. 30 dog, ligation of the left branch of the portal vein was followed by that of the 3 hep. aa.. When the former was ligated, the region that receives blood supply from the vessel immediately became dark red and swollen. Then, by the ligation of the 3 hep. aa., it got more dark. This dog survived and was sacrificed 2 weeks later. The anterior two-thirds of the left inferior lobe, which receives blood supply from the ligated portal branch, showed necrosis which was clearly demarcated off from the normal region. Histologically, the affected area showed anemic widespread necrosis, while the rest remained almost normal.

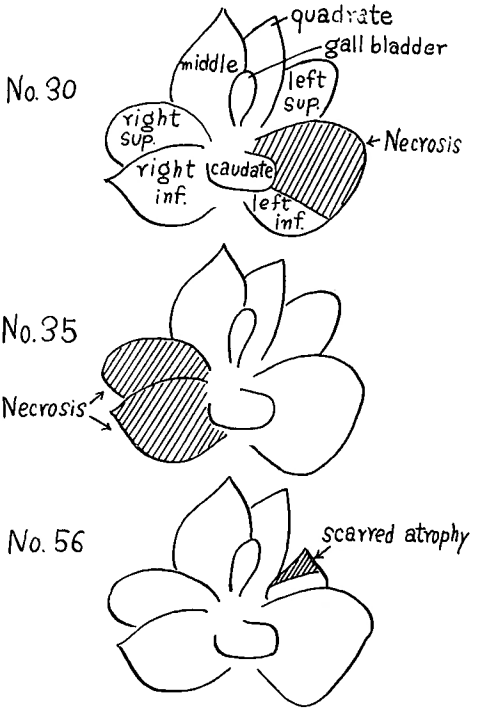


Fig. 1

No. 35 dog died 2 days after the ligation of right portal branch and 3 hep. aa.. Anemic necrosis was found completely covering the whole region of the right sup. and inf. lobes, which had been deprived of blood supply by the ligation. Hemorrhagic necrosis were seen here and there in other lobes.

2. Dogs with Injection of Millet Seeds (Table 2)

Table 2 Dogs with injection of millet seeds

Dog No.	Weight	Sex	Approximate number of millet seeds injected	Days from injection till ligation	Days from ligation till death	Result
44	9.6kg	♀	60	8 days	1 days	Death
54	10.3	♂	20	20	6	Death
57	7.0	♂	10	17	10	Sacrifice
58	10.0	♂	30	8	1	Death

In No. 58 dog, immediately after the injection through the mesentric vein, the liver surface began to show dark red marks of congestion. After a week, laparotomy revealed many congested areas on the surface. These areas caved in slightly and were sharply circumscribed from the surrounding tissue. The histological picture of these areas was that of ZAHN infarct (Fig. 2). When the 3 hep. aa. were ligated and 100,000 units of Pc was injected into the peritoneal cavity, the animal died 20 hours postoperatively. At autopsy the liver surface showed a complex combination of different colors like dark reddish brown, white and others, as well as ZAHN infarct (Fig. 3). Histological findings of the areas with dark reddish brown color were congested or hemorrhagic necrosis, while those of the areas with white

color were of anemic one. Observation was made on the cut surface of the succesive slices of the liver (about 5 mm thick). Injected millet seeds were observed to have been distributed all over except in the periphery of the liver. One cut surface showed a wedge-shapedarea of ZAHN infarct with a millet seed in its vertex (Fig. 4).

In No. 44 dog, the right sup, and inf. lobes had more millet seeds and consequently more marked congestion or hemorrhagic changes than the other lobes. In addition, there were many white rings in the liver, 3 to 10 mm in radius, which encircled the vassels blocked by the millet seeds, and perivascular regions showed a complex combination of different colors due to infiltration of green bilious pigment (Fig. 5). The white portions were areas of anemic necrosis histologically (Fig. 6). In No. 54 dog the millet seeds were found only in the right sup. and inf. lobes. The liver showed no color change after the injection. Nor did postmortem examination on its sliced surfaces disclose any particular changes around the millets, except for general congestion (Fig. 7). The periphery of the left and middle lobes, however, suffered from anemic necrosis, regardless of the injected millet seeds.

On the contrary, No. 57 dog had millet seeds chiefly in the left lobe. This dog only survived healthily.

As is understood from the above, distribution of emboli, caused by the millet seeds injection, amog different lobes so varied by cases that any generalization was impossible (Table 3).

Table 3 Distribution of emboli caused by millet seeds

Dog No.	right inf. lobe	right sup. lobe	middle lobe	quadrate lobe	left sup. lobe	left inf. lobe	caudate lobe
44	++	++	+	+	+	+	+
54	++	++	−	−	−	−	−
57	+	−	−	−	++	++	−
58	+	+	+	+	+	+	+

3. Dogs with Injection of Lycopodia (Table 4)

Table 4 Dogs with injection of lycopodia

Dog No.	Weight	Sex	Injected amount of solution containing lycopodia	Day of ligation	Days from ligation till death	Result
42	9.4 kg	♀	5 cc	10 days after injection	2 days	Death
43	13.0	♀	8	Immediately after injection	6	Death

In No. 42 dog, no sooner had 5 cc of saline solution saturated with lycopodia been injected through the mesentric vein than many dark reddish spots of congestion appeared on the liver surface. The anterior parts of the left sup., middle, right sup. and inf. lobes especially became dark red and swelled all over. After 10 days the 3 hep. aa. were ligated, which resulted in death of the animal 2 days later.

In No. 43 dog, injection of 8 cc of the similar solution was immediately followed by the ligation of the 3 hep. aa.. The injection caused no color change but a few narrow, dark reddish marks on the liver. The dog died 6 days postoperatively,

revealing the whole liver generally congested. Histological examination disclosed areas of anemic necrosis demarcated by cell infiltration, as well as those of congestion, hemorrhage and hemorrhagic necrosis (Fig. 8). The lycopodia was found scattering in portal veins in GLISSON's capsules and in sinusoids (Fig. 9).

III Discussion (Table 5)

Table 5 Postoperative course of non-infectious livers with ligation of hep. aa.

Portal circulation impediment → Congestion → ZAHN infarct
Congestion → Hemorrhage → Hemorrhagic necrosis

Portal circulation impediment with simultaneous ligation of hep. aa. → Anemic necrosis
→ Hemorrhagic necrosis

Portal circulation impediment followed by ligation of hep. aa. after a while
→ Congestion
→ Hemorrhage
→ Hemorrhagic necrosis
→ Anemic necrosis
→ Zahn infarct

The above preliminary experiment has made it clear that in whatever portion of the intrahepatic portal vein circulation impediment may be caused to occur, there develops congestion followed by ZAHN infarct, and that, when intensely impeded, congestion is followed by hemorrhage and then hemorrhagic necrosis.

When portal circulation impediment was accompanied with the ligation of the 3 hep. aa., anemic necrosis occurred because the blood supply to the area of blocked portal vein, both arterial and venous was entirely interrupted. When interruption of the portal blood flow is incomplete according to the degree or the position of the circulation impediment, a simultaneous ligation of the hep. aa. may cause hemorrhagic necrosis.

If the ligation of the hep. aa. was performed a certain period of time after the formation of portal circulation impediment, complicated findings were obtained, with congestion, hemorrhage, hemorrhagic and anemic necrosis, and ZAHN infarct all mixed up.

URABE, in our clinic, has proved that when a ligation of the 3 hep. aa. onl yis performed on normal dogs with postoperative administration of penicillin, the mortality rate is about 30%. Whereas, the above preliminary experiment disclosed as high a mortality rate as 78% after the ligation of the hep. aa. in the dogs with portal circulation impediment. This may be assumed that it was the intrahepatic portal circulation impediment that advanced a development of liver necrosis, a principal cause of the death after the ligation of the hep. aa.. So complex is the relationship of the degree of circulation impediments to the fate of the dog with the ligation of the hep. aa., that no simple generalization is possible. As is inferred from the above findings of the dogs with ligation of a portal branch, however, it seems that the fate of the dogs depends upon how large an area of the liver suffers

portal circulation impediment. According to POPPER, dogs survive when the proportion of the necrotic area against the whole liver is less than 1/3, while they die when it exceeds 1/2. The data obtained from the present experiment agree with him.

CHAPTER III MAIN EXPERIMENT

— Infectious Thrombosis —

I Methods

Clinically, the most important cause of intrahepatic portal thrombosis is bacterial infection of the liver. Therefore, in the present study the following different methods of infection were employed to cause thrombosis in the liver.

Gelatine-cultured colon bacilli and staphylococci were used for the present purpose. The amount of the bacteria used at a time was about 1 to 20 platinum loops.

Methods of Infection:

a) Ascending infection

1) Cholecysto-jejunostomy with BRAUN's anastomosis. Abbreviation: C.J.M.B. (9 cases were operated on ····· 5 cases survivals)

2) Cholecysto-jejunostomy without BRAUN's anastomosis. C.J.O.B. (10 cases··· ···4 survivals)

3) Injection of colon baclili through the common bile duct and constriction of the common bile duct. (Incision of the duodenum exposed the papilla of VATER, through which a vynyl tube was inserted into the common bile duct. Immediately after a saline solution containing the bacilli was injected through the tube, it was taken off and the common bile duct was constricted with a silk suture.) (Fig. 10) Coli (Ch). (9 cases·····3 survivals)

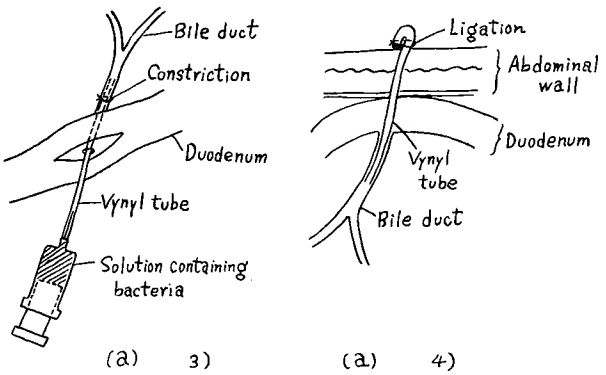


Fig. 10

4) Injection of colon bacilli through the common bile duct and temporary constriction of the duct. (One end of the vynyl tube for injection of the bacilli was blocked and fixed to the abdominal wall, making bile-flow stagnant, and then was taken off.) (Fig. 10) Coli (Ch'). (6 cases ·····2 survivals)

5) Injection of staphylococci through the common bile duct and constriction of the duct. Staph (Ch). (1 cases……none survival)

b) Haematogenous infection

1) Injection of colon bacilli through the mesentric vein. Coli (V.P.). (4 cases……3 survivals)

2) Injection of staphylococci through the mesentric vein. Staph (V.P.). (7 cases……4 survivals)

3) Injection of rabbit's liver-adapted strain of Staphylococcus aureus (F.D.A.) through the subcutaneous vein. (1 cases……none survivals)

II Results (Table 6)

Table 6 Infectious dogs I

Dog No.	Sex	Weight	Method of infection	Days till ligation	Days till death	Survival or death	Weight of liver	Weight of spleen	Weight of kidney	Macroscopic view Necrosis	Abscess
1	♀	10.5kg	C. J. m. B.	64days	39days	S	500g			−	(+)
2	♀	9.0	C. J. m. B.	126	37	S	400			−	−
4	♂	12.5	C. J. m. B.	38	5	D	500			##	−
6	♀	8.0	C. J. m. B.	53	8	D	390			##	+
8	♂	13.0	C. J. m. B.	66	19	S	500			−	−
15	♂	10.8	Coli (Ch.)	12	3	D	400			+	−
16	♂	9.2	Coli (V.P.)	8	1	D	410			#	−
17	♂	10.2	Coli (V.P.)	17	15	S	350	30g	30g	(+)	−
18	♂	12.0	Coli (V.P.)	21	18	S	590	32	50	−	−
23	♀	7.0	Coli (Ch.)	22	12	S	265	28	17	−	−
24	♀	7.0	Coli (Ch.)	23	1	D	390	25	30	##	−
28	♀	9.6	Coli (Ch')	44	1	D	430	30	30	+	+
29	♀	11.5	Coli (Ch')	38	1	D	370	50	30	+	−
38	♀	9.0	C. J. O. B.	70	44	S	320	30	25	−	−
39	♀	9.0	C. J. O. B.	65	1	D	300	40	35	+	−
40	♂	9.6	C. J. O. B.	101	17	S	330	30	40	−	−
41	♀	12.3	C. J. O. B.	105	2	D	520	50	40	#	−
45	♂	9.8	Staph.(V.P.)	21	1	D	370	30	40	+	−
49	♀	6.7	Staph.(V.P.)	47	2	D	190	10	20	#	−
51	♀	7.0	Staph.(V.P.)	45	2	D	260	20	25	#	−
52	♀	7.6	Staph.(V.P.)	45	10	S	380	25	20	−	−

The procedures for infection were performed on 43 dogs, 22 of which died halfway, while the rest 21 went through the whole course of the procedures (Table 7). In these 21 dogs the hep. aa. were ligated after a period enough for portal thrombosis to develop, that is, 8 to 126 days. Some of them went further to undergo cholecystectomy.

On gross observation at the time of the ligation, the liver appeared almost normal. In many cases the liver lobes were found adherent to each other or to adjacent viscera, particularly on their inferior surfaces. Changes clearly identified as ZAHN infarcts caused by thrombosis were seldom found. In the cases of severer infection,

Table 6 Infectious dogs Ⅱ ——Microscopic view——

Dog No.	Inflammatory reaction			Hepatic cells		Portal thrombi	Disarrangement of cell cords	Enlargement of sinusoids	Hemorrhage	Fibrous changes	Proliferation of bile duct	Bile thrombi
	Interstices	Lobules	Abscesses	Degeneration	Necrosis							
1	++	+	+	++	−	−	+	−	−	++	+	−
2	+	±	+	−	−	−	+	+	+	+	+	−
4	+++	+++	++	++	+++	+	++	+++	+	++	+	+
6	+++	+++	++	++	+++	+	++	+++	+++	++	+	++
8	+	±	−	−	−	−	−	−	−	+	+	−
15	+	+	−	+++	+	+	+++	+	+	+	+	++
16	++	++	−	+	+	+	++	++	++	−	−	−
17	++	+	+	+	+	+	+	+	+	−	−	++
18	+	±	−	−	−	−	+	++	±	−	−	−
23	+	−	−	−	−	−	−	+	−	−	+	−
24	++	+	−	++	+++	+	++	++	+++	++	++	+
28	+++	++	+	++	+++	−	++	+++	+++	+	++	−
29	++	+	−	+	++	−	++	++	++	+	+	−
38	+	+	−	−	−	−	+	+	−	−	+	−
39	++	+	−	++	+	+	++	+	+	+	+	−
40	+	+	−	+	+	−	+	+	−	+	+	−
41	+	+	−	+	+++	+	+++	++	−	++	+	−
45	++	++	−	+	++	+	++	++	+	+	−	−
49	++	++	−	+	++	+	++	++	+	+	−	−
51	++	+	−	+	++	−	+	+	++	−	−	−
52	+	−	−	−	−	−	−	−	−	−	−	−

Table 7 Prognosis of dogs on which infection procedures were performed

Died half-way	22
Peritonitis	5
Hepatic abscess	5
Cholangio-hepatitis	2
Distemper	6
Damages caused by operation itself	4
Survivals	21
Totals	43

multiple abscesses developed, causing death in most of the dogs before the ligation. And in all these cases autopsy disclosed that the liver surface was like a map complicatedly patterned with areas of dark reddish brown or yellowish brown, and that there were milletlike or tree-shaped abscesses scattered over the cut-surfaces of the liver. In these cases, however, in spite of so severe inflammation, such typical ZAHN infarcts, as were seen in the cases with injection of millet seeds, were not found. In other words, complete thrombi scarcely appeared when inflammation existed in comparatively thick portions of the intrahepatic portal vein. The only exception among the 5 dogs which had abscesses was No. 21 dog in which thrombosis was clearly noticed (Fig. 11).

As the 3 hep. aa. were ligated and 100,000 units of Pc was injected into the peritoneal cavity, 9 dogs out of the 21 survived, while the rest died between 1 and

8 days postoperatively. The mortality rate was 57%, about twice as high as that of 30% in the cases of the dogs without infection. All the dogs that died had bloody purulent ascites in the peritoneal cavity. As for the proportion of the weight of the liver, spleen and kidneys to that of the body, there was no marked difference between 2 groups that died and survived (Table 8).

Table 8 Proportion of weight of liver, spleen and kidney against body weight

	Weight of liver/Body Weight	Weight of spleen/Body weight	Weight of kidney/Body weight
Survival group	4.12 %	0.320	0.316
Dead group	4.02	0.350	0.348

As for the liver, gross observation at the time of death, however, revealed a significant difference between the two groups. In the group that died, all had more or less massive necrosis (Fig. 12), while in the other, any changes suggesting necrosis were hardly observed, with the exception of No. 17 dog which had local peritonitis caused by perforation of the gallbladder, and in which necrotic changes were seen only locally around the perforated organ.

Abscesses were found on the surface or the sliced surface of the liver scatteringly, in No. 6 and No. 28 dogs of the dead group, and only locally in No. 1 dog of the survival group. All those dogs, which had highly developed abscesses, had died before the ligation of the hep. aa..

To search for thrombi, the livers were cut with a transplantation-knife into slices about 5 mm thick, upon which gross observations were made. It was, however, difficult for the naked eye to identify them. What is worse, on such conditions, they were all so fresh and new that it seemed difficult and sometimes impossible to distinguish them from postmortem blood coagulations often seen in the portal vein. Therefore, histological examinations were made for the present purpose.

Histological Findings

The liver, spleen, kidneys, lungs and other organs were taken out from the dogs within 20 hours after they died or were sacrificed. The tissues were fixed in formalin, stained by hematoxylin and eosin, and then examined histologically.

The degree of inflammatory reaction was judged chiefly by that of leucocytic or round cell infiltration. In all dogs with the infection and the ligation, inflammatory reaction was seen more or less. In some of them, both parenchyma and interstice suffered cell infiltration almost evenly, in the form of cholangio-hepatitis, but in most of others inflammation was severer in interstice than elsewhere, gradually spreading over parenchyma (Fig. 13). Inflammation of the interstice was such that cell infiltration was seen at an early stage in and around the bile duct in the group with ascending infection (Fig. 14), and in the wall of the portal vein and periportal areas in the group with haematogenous infection (Fig. 15). But soon the inflammation further spread over GLISSON's capsules around, and there came to be no difference in appearance between the two groups. In those cases where inflammation was severe, abscesses were observed here and there along GLISSON's capsules.

Which of the methods of infection entailed what degree of infection? To answer this question; the mortality rate is the same with the ascending method as with the haematogenous method, as a whole. But so far as the ascending method are concerned, mortality rate was higher when bacteria were injected directly from the common bile duct and bile was stagnated than when the infection was naturally caused by the cholecysto-jejunostomy. In the cases of the haematogenous infection, staphylococci showed a stronger infectious power than colon bacilli (Table 9).

Table 9 Methods of infection and degrees of infection

		Survival	Death
Ascending infection.	C. J.	5	4
	Coli (Ch)	1 } 1 } 6	2 } 4 } 8
	Coli (Ch')	0	2
Hematogenous infection.	Coli	2 } 3	1 } 4
	Staph.	1	3

The degree of degeneration or necrosis of liver cells was roughly speaking in direct proportion to that of inflammation. Therefore, in the dead cases, changes were marked always with massive necrosis, while in the surviving ones necrotic changes, if observed, were chiefly centrilobular (Fig. 16). In many cases, areas of ishemic necrosis and those of hemorrhagic necrosis were found alternating with each other. No. 15 dog, necrosis was of a comparatively slight degree, but there was prevailing a high degree of cell degeneration indicated chiefly by a cloudy swelling of cells (Fig. 17).

Disturbed arrangement of liver cell cords, enlargement of sinusoids, congestion and other changes were observed in nearly all cases, and their degrees were generally in proportion to that of infection. Where congestion was intense, hemorrhage occurred in the center of lobules, pressing liver cells to degenerate into necrosis. In cases with ascending infection, proliferation of the bile duct and bile thrombi were often seen.

Now concerning thrombosis, several cases were inquired. Fig. 18 and Fig. 19 show a thrombus at an early stage, clinging to the inside of the vascular wall. In the latter picture, reaction of fibroblasts is shown about to occur. Fig. 20 shows organization of a thrombus originating from that part of the vessel wall to which it is adjacent. Fig. 21 reveals a thrombus chiefly composed of fibrin, with only elastica left in the wall. Fig. 22 shows a thrombus turned into necrosis at the early stage of its organization and there are seen debris of nuclei, regeneration of capillary vessels and cell reaction. Fig. 23 shows an infectious thrombus with its organization and regeneration of capillary vessels. Fig. 24 shows a separating thrombus composed of fibrin with erythrocytes, leucocytes and others attached to them; it shows a tendency of organization, invasion by endothel cells, and recanalization by regenerated capillary vessels. Fig. 25 shows thickening of the hepatic arterial wall and proliferation of endothel cells, without signs of formation of thrombi.

As seen in the above cases, in the infectious livers, especially in those severely infected livers of the dogs that died, chiefly portal thrombosis of various degrees was observed. Although it would be easy to identify thrombi if their organization

has progressed to a considerable degree, those thrombi observed in the present experiment were mostly so fresh and new that it was often difficult to distinguish them from postmortem coagulations. To take Fig. 26 for example, it shows only erythrocytes filling the portal vein, but the proliferation of endothel cells of the vascular wall (Fig. 27) proves that the erythrocytes had been collected there to form a thrombus 2 or 3 days before the death, which caused endophlebitis and proliferation of endothel cells. In Fig. 28, projections within the vessels are PAS-positive matters as a vital reaction of the wall due to the thrombus. To identify thrombi, not only their organization but also changes in the vascular wall should be taken into consideration. It is obvious from the above histological examinations that the 3 changes, that is, inflammatory reaction, development of thrombi and necrosis of hepatic cells, are closely related to each other, and that their degrees generally go parallel : In the surviving dogs all these 3 changes were of a slight degree, while in the bogs that died they were of a high degree.

In order to see in what portions of the liver which of the 3 changes would be remarkable, observations were made on the distribution of thrombi, of massive necrosis and of inflammation among different lobes of those dogs that died with more serious changes (Table 10). The results are; in the infectious livers, just as

Table. 10 Distribution of massive necrosis (○), thrombi (□) and degree of infection (+. ++. +++)

Dog No.	right inf.	right sup	middle	quadrate	left sup.	left inf.	caudate
4	+	+	⊞	+	++	⊞	++
6	⊞	++	+++	++	++	⊞	++
15	⊞	+	+	+	⊕	⊕	+
16	++	++	⊕	⊕	⊕	⊞	⊕
24	+	+	⊕	+	++	⊞	⊞
28	++	++	+++	+++	+++	+++	+++
29	++	++	++	++	++	++	++
39	++	++	++	⊞	++	⊞	++
45	++	⊞	++	++	++	⊞	⊕
49	+	+	++	++	++	⊞	⊕
51	⊕	⊕	⊕	⊕	⊕	⊕	⊕

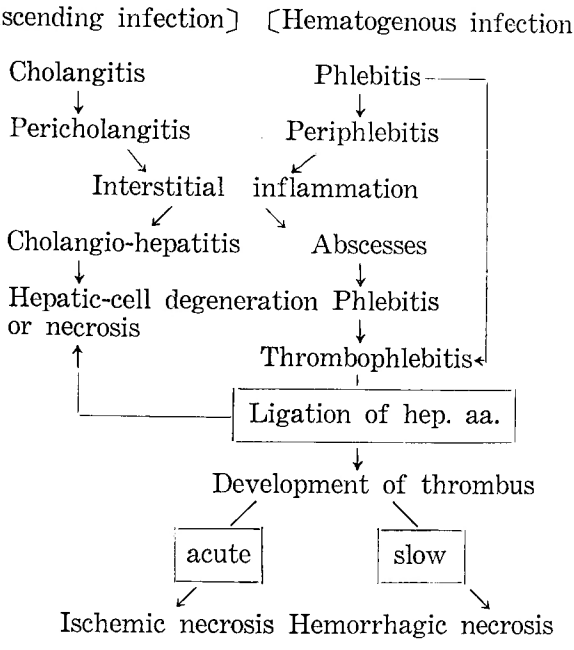
in the non-infectious ones, necrotic lesions were most likely to occur in the left inf., caudate, and middle lobes, where inflammation was generally severer, most thrombi exclusively gathered there and abscesses were sometimes formed. In other words, the degrees of the 3 changes broadly went parallel also in the case of each lobe of each individual liver. In those dogs which died of liver abscesses before the ligation of the hep. aa., however, no such limited spread of inflammed areas among different liver lobes as was seen in the surviving dog was found……that is, inflammation was encountered equally in all liver lobes. In these dogs, thrombi were so few for the high degree of inflammation, and in most cases, the liver showed no greater changes than phlebitis. From the above, it may be concluded that the difference in the distribution of the 3 changes among different liver lobes comes from the diffe-

rence in the portal circulation impediment after the ligation of the hep. aa..

III Discussion

The above observations made on the infectious liver after hepatic arterial interruption have made it clear that the changes in the liver are generally as follows (Table 11) : Infection spreads first over GLISSON's capsules after cholangitis and

Table. 11 Postoperative course of ifectious liver after ligation of hep. aa.



pericholangitis in the case of the ascending infection, and after phlebitis and periphlebitis in the case of the haematogenous infection. When inflammation is severe, multiple small abscesses are formed along GLISSON's capsules. As inflammation or abscesses invade the wall of the portal veins, phlebitis and then thrombophlebitis occur, and sometimes endoarteritis of the hepatic artery or endophlebitis of the hepatic vein is brought about, with thicking of the vascular walls and proliferation of endothel cells, but scarcely any thrombi are formed. It is, therefore, reasonable to assume that formation of thrombi occurs exclusively in the portal tree.

In some portal thrombi, organization advanced to such a degree as recanalization had been brought about. These thrombi seems to have already existed before the ligation of the hep. aa.. Investigators in our clinic have proved that the ligation of the hep. aa. immediately brings about a marked degree of stagnation of the portal flow. It is, therefore, evident that such a sudden decrease in the velocity of the portal flow promotes a rapid formation of thrombi, particularly in those infectious livers whose vascular walls have already encountered inflammatory changes. This makes us assume that most fresh thrombi were produced in this way, and it

is also natural that they should easily develop in areas of marked congestion, and consequently in areas where necrosis is more likely to occur.

Now turning to the development of necrosis that goes parallel with formation of thrombi after the ligation of the hep. aa., it seems that when a thrombus suddenly develops in a comparatively thick vessel, both the arterial and the venous blood supply is at the same time interrupted to cause ischemic necrosis, while if a thrombus develops either slowly or in a comparatively thin vessel which anastomoses with another one, hemorrhagic necrosis occurs (Fig. 29). In the former case, the necrotic areas have no cell reaction, and are sharply circumscribed by a cell infiltration line (Fig. 30). In the latter, congestion, hemorrhage, parenchymal degeneration generally caused by compression and finally necrosis occur extending from the center to the periphery of the lobules, with adjacent lobules fused together; cell reaction is seen in the foci of necrosis; and demarcation between the normal and the damaged areas is not so sharp as in the former case, but very obscure (Fig. 31).

It may be added that in the infectious livers, the infection was not limited to GLISON'S capsules but spread over the parenchyma, taking the form of cholangiohepatitis, sometimes with cell degeneration such as cloudy swelling and fatty degeneration of the cells (Fig. 32). In such cases, liver dysfunction should not be depreciated as a cause of death. According to liver function tests we had done, the values of B.S.P. and MEULENGRACHT remained within normal in both the dead and the surviving dogs (Table 12). This means that liver dysfunction caused by hepatic

Table 12 Liver Function

Dog No.	Time of test	B. S. P.	M. G.	Prognosis
38	70 days after C. J.	20′ : 0% 45′ : 0	3	Survival
39	65 days after C. J.	20′ : 2.5 40′ : 0	3	Death
40	101 days after C. J.	25′ : 0 45′ : 0	3	Survival
	After ligation	40′ : 0	3	
41	105 days after C. J.	20′ : 5 50′ : 0	4	Death
45	21 days after Staph. (V. P.)	20′ : 5 45′ : 2.5	2	Death
49	Before ligation	20′ : 3.5 40′ : 0	2	Death

〔Normal dogs B. S. P. 20′ : 0～5 %
45′ : 0～2.5% Tsuchiya〕

cell degeneration cannot be assumed to have been a immediate cause of death. In the other viscera of the infectious dogs, such as the spleen, kindneys, lungs, intestine etc., any marked changes suggestive of immediate causes of death were not observed on either gross or histological examination, except for congestion, hemorrhage and a slight degree of infection. From this it is concluded that just as in the non-infectious dogs, the immediate causes of death of the infectious dogs are anoxic necrosis that develops after hepatic arterial ligation, and the function of Lecithinase produced by anerobic bacteria that bred in the anoxic areas. (YAMABE)

Chapter IV SUMMARY

It has been clarified through the experiment, no matter whether infection occurs or not, the existence of intrahepatic portal thrombosis is closely related to development of liver necrosis after the interruption of the hepatic aa., and consequently to the mortality rate of the dogs operated upon. When both 8 dogs with non-infectious portal circulation impediment and 21 dogs with it are put together, the mortality rate is 61%, a figure about twice as high as 30% of normal dogs (Table 13).

Table 13 Mortality rate of dogs with ligation of hep. aa. (Penicillin-treated)

Normal dogs	30%	
Dogs with non-infectious portal circulation impediment	78%	61%
Infectious dogs	57%	

According to LUBARSCH, the significance of bacterial infection to the formation of thrombosis consists in (1) impeding the heart function and the vasomotoric center……decrease in the velocity of the blood flow, (2) having the functions of hemolysis and of dissolving cells……changes of the nature of blood, and (3) causing inflammatory changes to the vascular wall……damage of the vascular wall. Further more, according to MIZUTANI, the primary significance of infection to the formation of thrombosis is that inflammation extends over blood vessels, causing pan-phlebitis; but thrombosis does not develop till a considerably high degree of inflammation has extended to the endothelium of the vessel.

In the present report also, there seem to be comparatively few instances where thrombosis had already been formed solely by infection before the ligation of the hep. aa.. As LUBARSCH asserts, if there is bacterial infection, even when thrombosis has not yet been formed, it is at least ready to come out. Under such conditions, a sudden stagnation of the portal flow caused by hepatic arterial ligation……another favourable condition for formation of thrombosis……may well promote development of portal thrombosis. This is why thrombosis occurs chiefly in the left inf., middle and caudate lobes where portal stagnation is prominent. Moreover, thrombosis, which has been caused by circulation impediment, in its turn makes the portal circulation impediment more serious, promoting necrosis. The close relationship of existence of thrombosis to development of necrosis may be clearly indicated by the fact that when circulation impediment occurs in the lobes other than those where necrosis is the easiest to occur, for example, in the right lobe as in Nos. 44, 54 and 35 dogs, necrosis also develops chiefly there in the right lobe.

It seems almost impossible to ascertain clinically the existence of intrahepatic portal thrombosis. However, when the liver shows some symptoms of infection, or when there is a strong doubt of infections of the biliary system such as cholelithiasis, it is to be presumed that thrombosis is always there, or at least ready to be, so the ligation of the hep. aa. had better be avoided.

CHAPTER V CONCLUSION

The ligation of the hep. aa. was performed on the dogs in which intrahepatic portal circulation impediment had been brought about with or without infection. Gross and microscopic observations were then made. The results are:

(1) In the liver of each dog with the ligation of the hep. aa., and in each lobe of the individual liver, the degrees of the 3 changes, that is, infection, thrombosis and necrosis went almost parallel. In those dogs which died as a result of the ligation, the degrees turned out generally high.

(2) When thrombosis existed in the portal vein, whatever its causes might be, postoperative development of liver necrosis was advanced, resulting in an increase in the mortality rate.

(3) In the infectious liver, even when no thrombosis has yet been formed, the ligation of the hep. aa. should be avoided clinically, because the portal vein is under such conditions that thrombosis is ready to develop.

In concluding my report, I wish to express my deepest gratitude to Dr. CHISATO ARAKI, professor of Kyoto Univ., Dr. ICHIO HONJO, professor of Kanazawa Univ. and IKUZO YOKOYAMA, assist. professor of Kyoto Univ. for their kind, continuous guidance, encouragement and supervision. Regarding histological findings, I am greatly indebted to Dr. YASUAKI NISHIZUKA, assist. professor of the pathological division, Kyoto Univ. Medical School for his kind guidance.

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和文抄録

肝動脈血流遮断による肝壊死に対する肝内門脈血栓の影響

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肝動脈遮断により門脈血行にも障碍を来し，この門脈血行障碍の帰趨如何が肝壊死の発生を左右することは，既に当教室で証明したところである．そこでもし肝動脈遮断前に既に肝内門脈枝に血行障碍のあるような場合，肝動脈遮断は非常に危険視される．この点を検討するため，感染其他各種方法で肝内門脈に血行障碍を作り，次でペニシリン投与を伴う肝動脈遮断を実施して，その予後に及ぼす影響を観察した．

Ⅰ 予備実験 —非感染性門脈血行障害について—

犬を用い，門脈分枝分岐部の結紮並に栗粒或は石松子の門脈内注入によつて，肝内門脈の各部に人工的血行障害を作製し，感染による複雑な干渉をさけて，血行障碍のみによる影響を検討した．これら血行障碍犬に於ては正常犬に比し，肝動脈遮断後，上記の前処置により血行障害を来した門脈流域等に壊死発生が顕著に見られ，従つて遮断後死亡率は，正常犬の約30％よりも高値を示した．

Ⅱ 本実験 —感染性血栓について—

肝内門脈血栓の形成原因として，臨床上最も重要な肝の細菌感染について検討するため大腸菌・葡萄状球菌等を使用し，上行性或は血行性に肝を感染せしめ，血栓形成を計つた．

組織学的検索によれば，感染肝に於ては，肝内門脈は炎症性変化の波及によつて，たとえ血栓形成に至らざる場合でも，既にその準備状態にあるものとみなされるが，かかる肝に肝動脈遮断を行うと，血栓の急激な発達を認めた．それは遮断後の門脈血行障害によつて，血栓形成が更に促進されたためと考えられる．又一般に肝の炎症反応・血栓形成・肝細胞壊死の程度は，三者大体比例した．

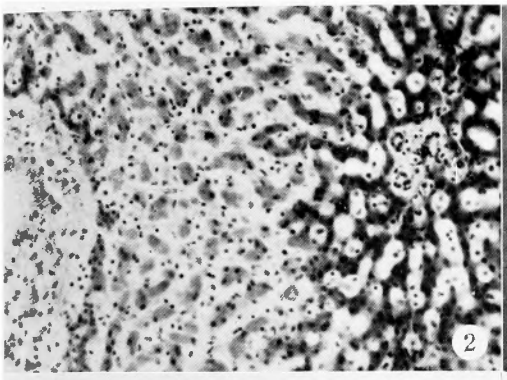
これら感染犬に於ても，遮断後死亡率は，正常犬の30％に対し57％の高値を示した．

Ⅲ 総 括

以上の諸実験を通して，如何なる原因によるものであれ，肝内門脈に血栓が存在するとき，肝動脈遮断後の肝壊死発生を容易にし，従つてその死亡率を増大することは明らかであり，非感染血行障碍犬8例と感染犬21例を合して考えると，死亡率は61％で，正常犬の死亡率30％の約2倍に当る．

臨床的に肝内門脈の血栓の有無を確証することは殆

んど不可能と思われるが，肝に何らかの感染症状の認められるとき，或は胆石症其他胆道系の感染が高度に疑われるときには，常に血栓形成或はその準備状態にあるものと考えて，肝動脈遮断は避けられねばならない．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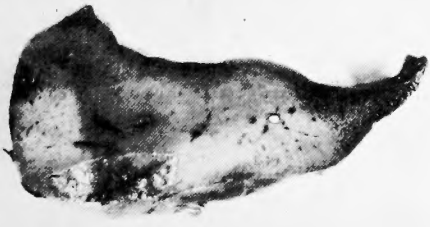
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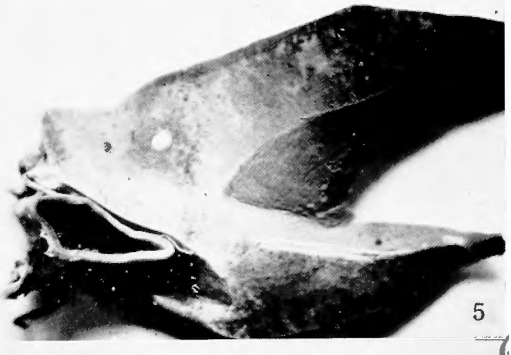
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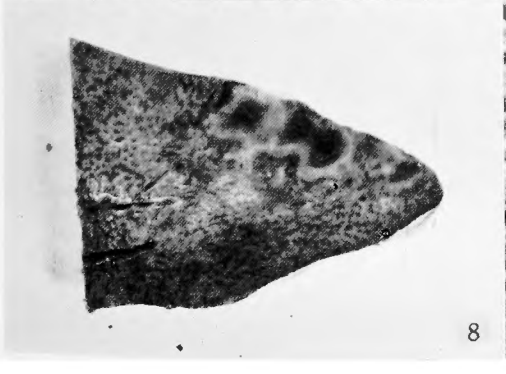
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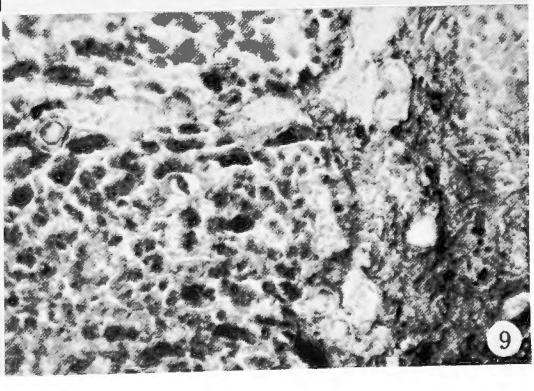
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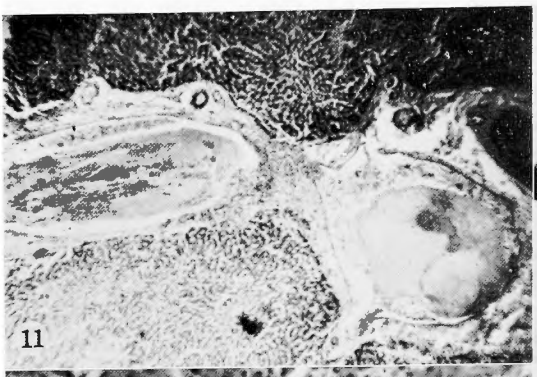
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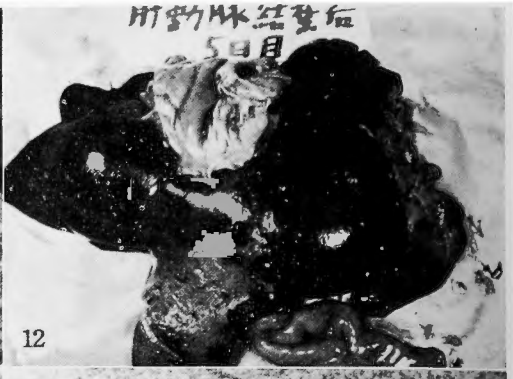

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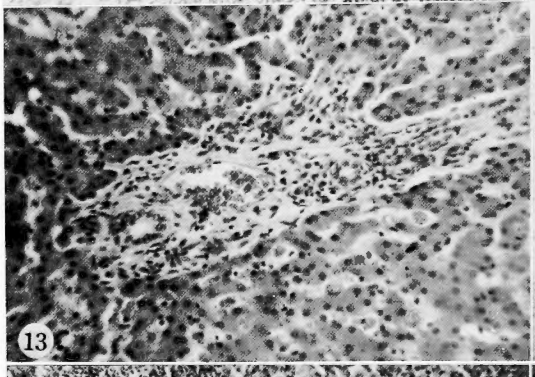
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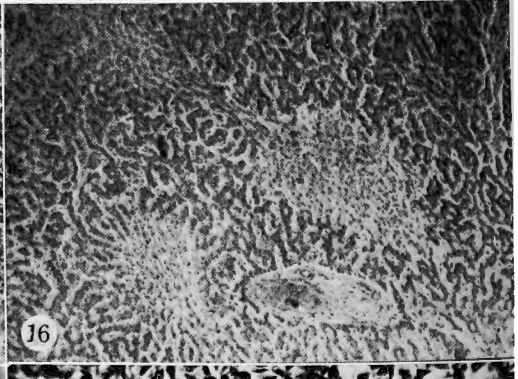
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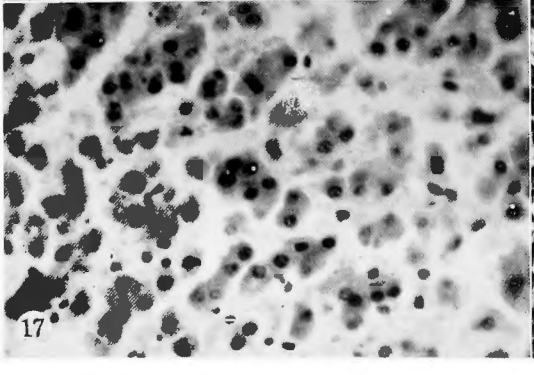
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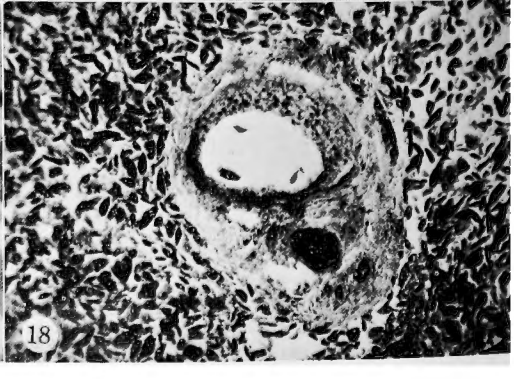
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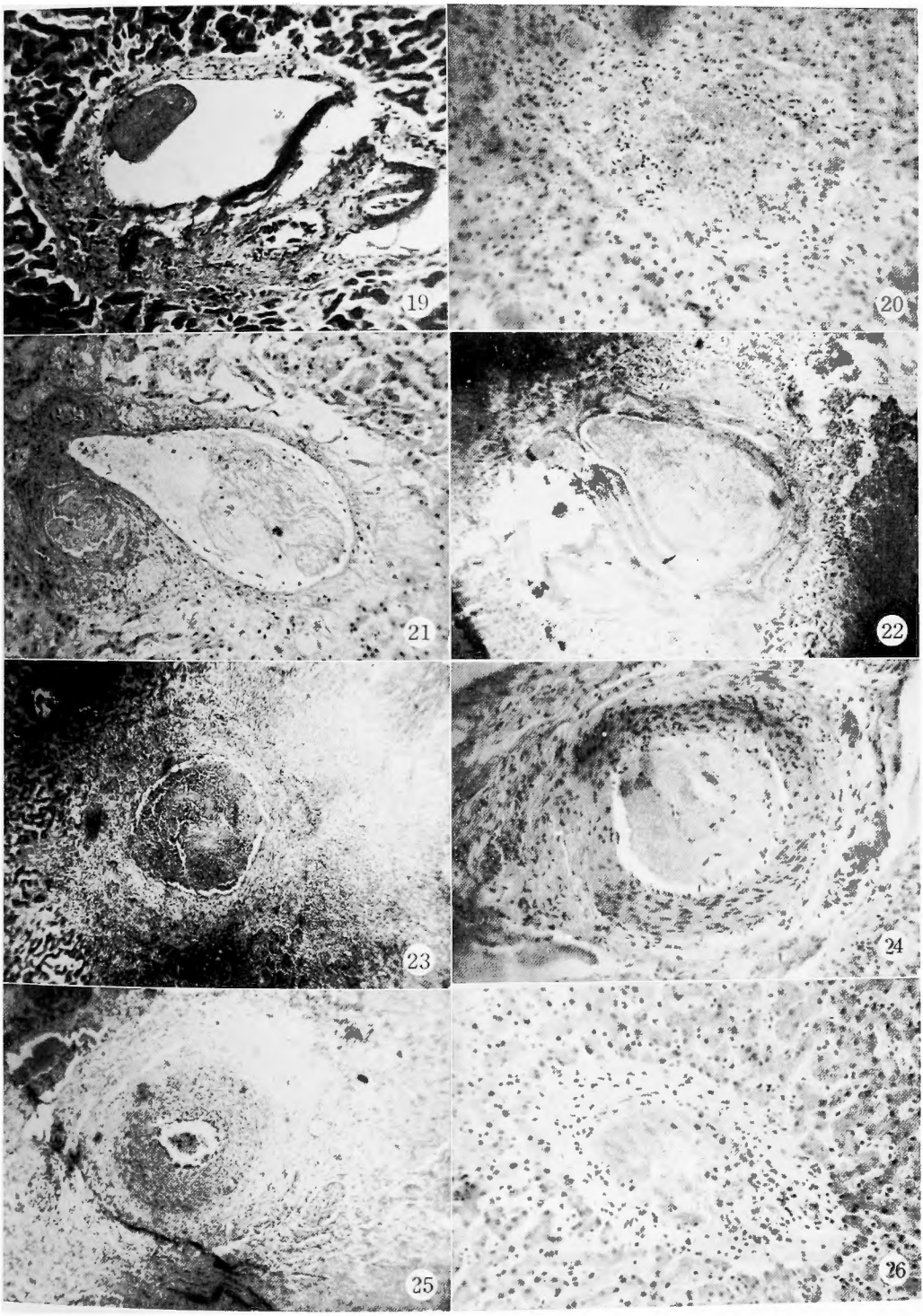
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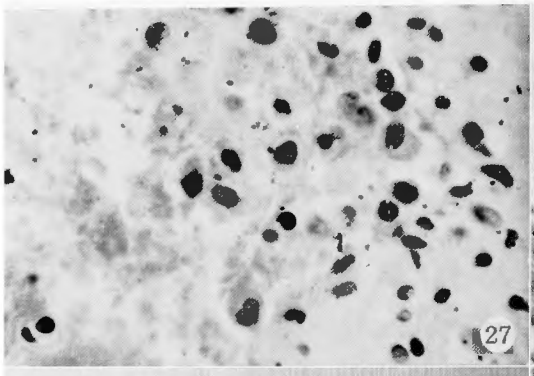
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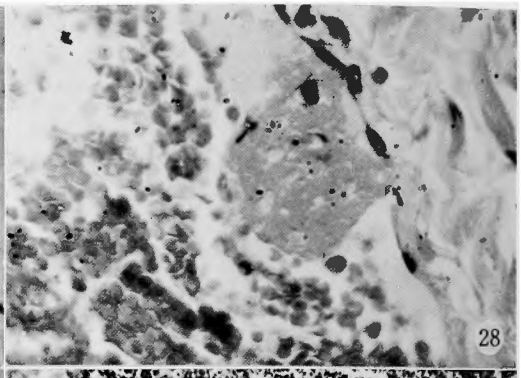
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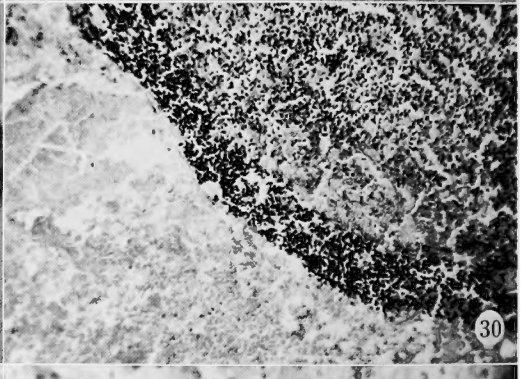
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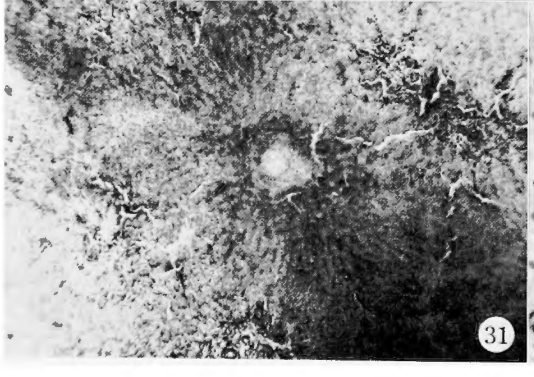
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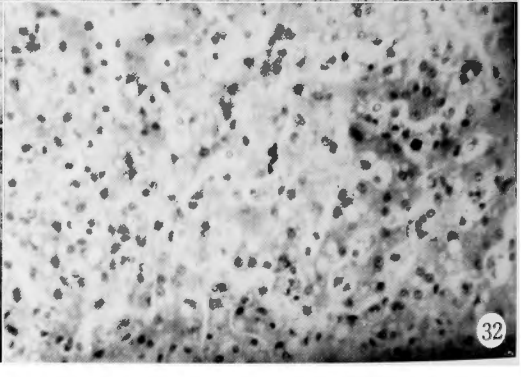
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